Air Pollution and Daily Mortality: A Hypothesis Concerning the Role of Impaired Homeostasis

Robert Frank and Clarke Tankersley

Department of Environmental Health Sciences, The Johns Hopkins University, Bloomberg School of Public Health, Baltimore, Maryland, USA

We propose a hypothesis to explain the association between daily fluctuations in ambient air pollution, especially airborne particles, and death rates that can be tested in an experimental model. The association between airborne particulates and mortality has been observed internationally across cities with differing sources of pollution, climates, and demographies and has involved chiefly individuals with advanced chronic illnesses and the elderly. As these individuals lose the capacity to maintain stable, optimal internal environments (i.e., as their homeostatic capacity declines), they become increasingly vulnerable to external stress. To model homeostatic capacity for predicting this vulnerability, a variety of regulated physiologic variables may be monitored prospectively. They include the maintenance of deep body temperature and heart rate, as well as the circadian oscillations around these set-points. Examples are provided of the disruptive changes shown by these variables in inbred mice as the animals approach death. We consider briefly the implications that the hypothesis may hold for several epidemiologic issues, including the degree of prematurity of the deaths, the unlikelihood of a threshold effect, and the role that coarse, noncombustive particles may play in the association. *Key words*: air pollution, homeostatic decline, mortality, particulates, vulnerability to stress. *Environ Health Perspect* 110:61–65 (2002). [Online 15 December 2001]
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Epidemiologic Background

Perhaps the most compelling evidence for an effect of low levels of airborne particulate matter (PM) on health comes from time-series regression analyses that link daily fluctuations in PM and mortality. The evidence is descriptive; the studies were retrospective, so variables could not be manipulated to test specific hypotheses. The approach, although powerful statistically, has rested on several premises: *a*) that a limited number of fixed outdoor monitors of air quality, a circumstance universal to these analyses, provided reliable estimates of exposure of the population-at-risk; and that adequate adjustments were made for both *b*) potential confounders, such as collinear air pollutants and changes in weather, and for *c*) cyclic factors that might modify mortality rate, such as day of the week and seasonal trends. Daily and seasonal changes in weather may affect mortality rate both directly and indirectly, the latter by influencing the physicochemical properties and ground-level concentrations of PM and of air pollution in general. The soundness of these underlying premises remains a matter of debate.

Is the association causal? Descriptive epidemiologic studies alone generally are viewed as insufficient to establish causation, especially if the estimated effect is small. They may, however, be used to infer causation. To justify the inference, a number of criteria should be met (*1–3*). Perhaps the most elusive of these criteria has been a biologic explanation or mechanism for the association (*4*). Indeed, weak biologic plausibility has been cited by Vedal (*5*) as "the single largest stumbling block to accepting the association as causal" (p. 558). Our objective (accepting the weight of the evidence as supporting a casual association) is to propose an explanatory hypothesis that, in accordance with Popperian principal, is refutable. We first briefly review salient features of the time-series evidence and their implications.

First, the association has been found among communities and nations that differed in their principal sources and composition of air pollution, including PM, as well as in climate. This would imply that no specific attribute of air pollution is an essential proximate cause of death and that an undefined number of such attributes may qualify as sufficient causes. Other forms of environmental stress, including meteorologic variables, may also qualify as sufficient causes (*6–8*).

Second, the association appears independent of population size and density. It has involved chiefly elderly persons with one or more chronic diseases, usually of the heart, blood vessels, or lungs. This would imply that failing health, attributable to aging or illness, largely defines the population at risk. As a corollary, the rest of the population is probably not at risk, especially at current levels of air pollution. And because the rate of physiologic decline can vary markedly among individuals, chronologic age is not a reliable index of vulnerability. However, one must be cautious regarding attributed causes of death. Death certificates can be one-dimensional, reporting only the disease that may have initiated a patient's decline while omitting contributory factors of importance. They may favor some specific causes over others, circulatory and respiratory diseases being among those most commonly overdiagnosed as the cause of death (*9,10*).

Third, the association, although consistent, has been small, explaining only a minor fraction of daily mortality. This would imply that the level of stress imposed by ambient PM is low or that the population at risk is small.

Among the domestic and foreign cities cited in three major reviews of such time-series studies, excess daily, nonaccidental mortality ranged between about 5% and 10% in association with an increase in ambient PM of 100 μg/m^3 (*11–13*). In the earlier studies reviewed, PM was measured as total suspended particulates (TSP) and in later studies as PM_{10} (i.e., the sampler had an upper 50% cut-point of 10 μm aerodynamic diameter). A more recent meta-analysis of data from the 90 largest U.S. cities confirmed this limited estimated effect: Overall, the daily excess mortality across these cities averaged about 0.5% per 10 μg/m^3 increase in PM_{10} with mean daily concentrations ranging between about 20 and 50 μg/m^3 (*14*). Accordingly, a typical U.S. city of 1 million inhabitants might experience a daily excess mortality attributable to PM of one to two deaths superimposed on an average of about 20 nonaccidental deaths (*15*).

Hypothesis

Homeostasis, the organism's capacity to withstand stress and maintain a stable, relatively constant internal environment, is most robust in young adulthood and declines with aging and illness. Biologic systems that are displaced only slightly from equilibrium, as

Address correspondence to R. Frank, Department of Environmental Health Sciences, Suite W6010, The Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Baltimore, MD 21205 USA. Telephone: (410) 614-5754. Fax (410) 955-9334. E-mail: rfrank@jhsph.edu

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in homeostasis, are well approximated by linear terms (*16*). The abundant interconnections among elements involved in sensing environmental change, internal as well as external, in distributing and storing this information, and in initiating a response underlie this stability. As this decline from aging or illness proceeds, the risk of dying increases. Stresses that can act as the proximate cause of death grow in number and variety, while the level of any particular stress sufficient to cause death diminishes.

We postulate, first, that for the population at large the curves of declining homeostasis and survival are closely linked, the former proceeding slightly in advance, as projected in Figure 1. The decrease in human survival rate beyond the initial inflection is exponential, doubling about every 8 years in conjunction with a rising mortality rate [Gompertz mortality function (*17*)]. The reverse inflection seen at more advanced ages (non-Gompertz mortality) has been attributed to the survival of a relatively homogeneous, robust subset of individuals (*18*). The initial period of homeostatic stability shown beginning in young adulthood is characterized by a gradual, roughly linear loss of physiologic reserve estimated to range between 0.5% and 1.3% annually (*19*). We are unaware of data that indicate an obvious inflection following the normal gradual decline. The rate of decline in pulmonary function as measured by the annual loss of the 1-sec forced expiratory volume does accelerate with advancing age: Depending on the statistical model used, the rate of decline may be about 4.5-fold greater at age 75 than at age 25 (*20*).The topography of survival is well documented. It appears similar for humans (*21,22*), rodents (*23*), and a variety of short-lived invertebrates (*24,25*) and may be considered generic. In general, four stages can be identified: an initial gradual linear decline followed by an inflection or transitional stage, an exponential decline, and, finally, a reverse inflection.

Second, the exponential stage of decline in the individual, as contrasted with the population, is likely to be monotonic. Terminal slowing or reversal of the rate of decline, equivalent to the non-Gompertz function characteristic of the survival curve for the population, is unlikely, except perhaps in association with some therapy that dramatically reverses or eliminates a severe illness.

Third, the exponential phase marks the spread of dysfunction among an increasing number of regulated systems. This feature is integral. The organism may be likened to a tightly integrated network of functional elements. Failure caused by aging or disease may initially be localized and accommodated; eventually other functional elements are entrained, failure becomes generalized, and survival is threatened. As a consequence, it is not unusual for individuals seriously ill from a variety of disorders, including senescence, to share common debilities (e.g., loss of body weight, impaired thermoregulation, electrolytic imbalances, postural hypotension, sleep disorders). Ultimately, the failing organism may exhibit a response to stress that is randomlike, nonlinear in dynamics, and more sensitive to its status at the moment a stress is experienced than to the form or intensity of that stress.

Such behavior has been referred to as "deterministic chaos" (*26,27*). Deterministic chaos is a theoretical construct, distinct from chaos as defined in a conventional dictionary. It is seen in stable organisms, especially among physiologic variables subject to nervous control, such as heart rate. It has been attributed, at least in part, to the innate complexity of the organism and the interplay—or competition—among its many elements. This interplay involves strategies such as feedback and feedforward. The effect is not only to constrain behavior but also to increase adaptability. Simplification of the system, through attrition imposed by aging and disease, acts to remove these constraints, reduce adaptability, and increase the probability of a fatal outcome (*28,29*). Deterministic chaos may account for the difficulty in time-series studies of identifying a threshold for the association between fluctuant levels of PM and mortality (*1,30,31*). Indeed, the concept of a threshold becomes problematic in the presence of such behavior.

Model Development

An empiric model of homeostasis should prove useful in identifying individuals whose decline has reached the acceleratory stage, when the risk of succumbing to modest levels of stress is heightened significantly. To develop the model, several fundamental attributes of the organism's steady state may be exploited. They are described below.

Stability. Many physiologic and biochemical variables are maintained within relatively narrow limits, often referred to as "set-points." The concept of physiologic set-points serves as a useful approach to understanding interactions among control systems of the body; these interactions may involve feedback, feedforward, adaptive, and even anticipatory strategies (*32,33*). Among variables with frequently cited set-points are body weight, deep-body temperature, heart rate, arterial oxyhemoglobin saturation, blood viscosity, and extra- and intracellular pH and salinity.

Periodicity. The same variables listed above may oscillate rhythmically on either a 24-hr (circadian) or seasonal basis. It is unclear how integrated or independent the homeostatic (relative constancy) and circadian (oscillatory) processes might be (*34*). The circadian oscillations, tuned through evolution, show remarkable short- and long-term stability (*35,36*), thereby underscoring their importance to well being. Disintegration of the circadian pattern with advanced aging and illness may influence the proximate cause and timing of death (*37,38*).

Rate and proportionality of response. A robust organism responds rapidly to newly imposed physical and metabolic demands.

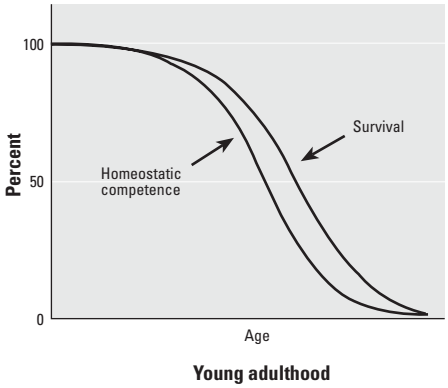

Figure 1. Projected relationship between homeostatic competence and survival within a population.

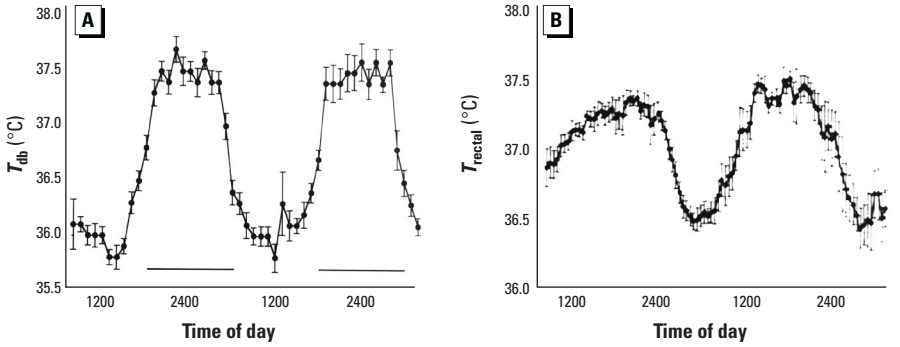

Figure 2. Comparison of circadian pattern of (*A*) deep-body temperature (T_{db}) in adult, male AKR/J mice (n = 9) and (*B*) rectal temperature (T_{rectal}) in healthy young men (n = 8). The lights-off period is indicated by the horizontal bar above the abscissa. [Reproduced from Scales et al. (*40*) with permission; the units of time have been changed to conform to those in (*A*)].

For example, the multisystem physiologic responses to the onset of exercise, thermal stress, or sudden changes in body position are all closely orchestrated in time and degree.

At present, we are monitoring several variables in AKR/J mice, a relatively short-lived, inbred strain, as a means of modeling homeostatic decline with aging and disease. The variables were selected for their simplicity, familiarity, and the means they provide for continuous monitoring without disturbing the animal, apart from the initial surgical implantation of a radiotelemeter. The care of and all procedures on the animals were in accordance with university guidelines and were described earlier (*39*). Here we present examples from our preliminary experience with two continuous variables, deep-body temperature (T_{db}) and electrocardiographic heart rate. The signals were obtained simultaneously.

Measurements of T_{db} and the electrocardiogram (ECG) were begun 14 days after the radiotelemeters were implanted. Data were collected beginning at 1700 hr on Friday through 0900 hr on Monday. Sampling duration was 15 sec; a mean value was calculated for every 30-min interval. The light/dark cycle was set on a 12-hr basis. The acrophase occurred in the mice during lights-off [2267 hr ± 71 min (SE)] and in the men during daytime [1724 hr ± 28 min (SE)]. The respective mean daily temperatures were 36.6 ± 0.1 and 37.0 ± 0.05°C. The respective mean temperature amplitudes were 0.40 ± 0.07 and 0.45 ± 0.06°C. In Figure 2A and 2B, the circadian pattern of T_{db} in mice can be compared with rectal temperature (T_{rectal}) obtained in a group of healthy human subjects. The tracings differ principally in the relationship of their peak-to-peak oscillations (acrophase and bathyphase) to the time of day; otherwise, they are similar.

An example of the changes in T_{db} that developed in one animal between the initial measurement made 14 days postoperatively and the last measurement made 24 hr before death is shown in Figure 3. Over the last 11 weeks of life, mean T_{db} fell about 9°C, while the circadian oscillations became irregular in amplitude. Progressive hypothermia before death has been seen in most animals studied to date. In humans, as mean T_{db} falls below 35°C, pathophysiologic consequences become more widespread and intense; the latter include changes in myocardial conduction and irritability (*41,42*).

Heart rate is plotted against age in Figure 4. The first group of animals had implants at 27 weeks of age; two additional animals from a separate cohort had implants at 10 weeks of age to provide a longer period of observation. The animal shown dying at 48 weeks of age, represented by red circles, was also the subject of Figure 3. Bradycardia and hypothermia in this animal had roughly similar onsets (i.e., 38th and 37th weeks, respectively). Of the four remaining animals, one was still alive with a well-maintained heart rate at 48 weeks, apparently an example of "successful aging" (*43*). Visual inspection suggests that heart rate may have been more stable early in adulthood (two animals from a separate cohort, with implants at 10 weeks of age) than in late adulthood before the inflection (five older animals). Changes in the variance of set-points or circadian patterns (timing and amplitude of the oscillations) hold promise as indicators of impending failure.

Comments

Our premise has two essential elements: that the population at risk of dying in association with daily fluctuations in air pollution consists chiefly of individuals with severe, generalized homeostatic instability, and that this instability, rather than the type or level of external stress, promotes the fatal outcome. The population at risk also includes individuals subject to sudden and unexpected cardiac death (SCD). Most cases of SCD are attributed to an ischemic event, superimposed on underlying coronary atherosclerosis, which triggers a fatal ventricular arrhythmia. A significant fraction of the victims are middle-aged and otherwise may appear in good health (*44*). Generalized failure may trace its origin to a variety of clinical disorders as well as to aging. To qualify as the proximate cause of death in such individuals, an external stress must be capable of initiating a response (an adjustment by a regulatory system) that involves the expenditure of energy. We believe the premise can be tested experimentally. The size of the at-risk population, how its size may influence exposure–response relations (daily mortality), and the degree of prematurity of these deaths all have implications for public health policy. As noted earlier, nonaccidental death is a rare event, so the population fueling this event can be presumed to be small relative to the population at large. Recently, Murray and Nelson (*45*) applied state-space modeling to mortality data from Philadelphia to estimate the size of this unobserved vulnerable population. Over a 14-year period, the vulnerable population averaged 480/year within a general population of about 1.5 million. A slight increase was noted toward

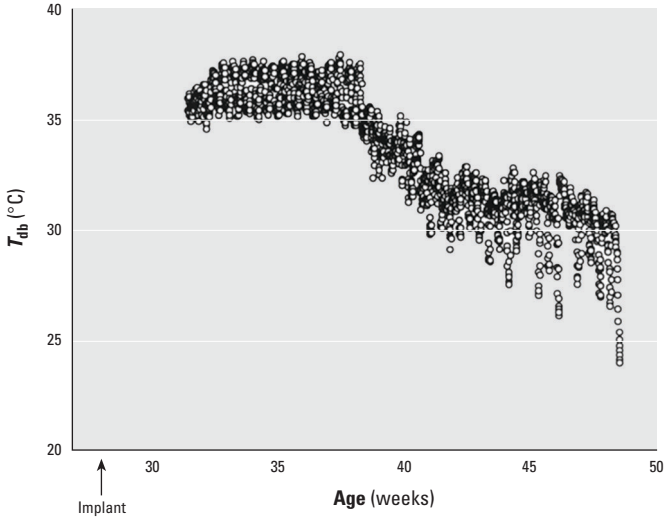

Figure 3. Loss of thermoregulation in an aging AKR/J mouse. The shift in thermal set-point and changes in amplitude of the circadian oscillation, represented by the thickness of the tracing, are apparent at about 37 weeks of age.

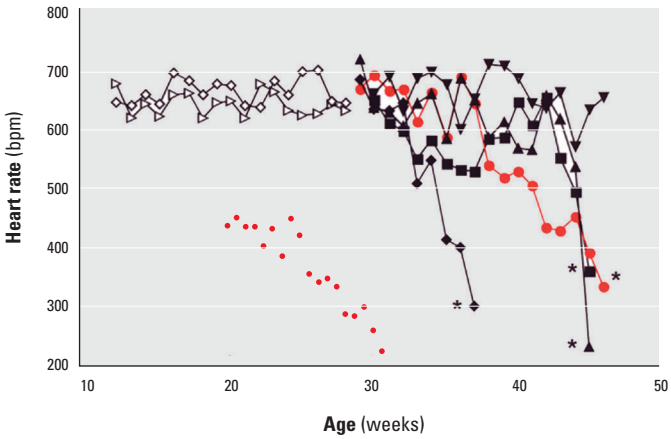

Figure 4. Daily mean heart rate plotted against age in AKR/J male mice (n = 7). The electrocardiogram tracing is analagous to lead II in humans. Solid symbols: first group of animals (n = 5); open symbols represent two animals from a separate cohort. The data shown were collected 1 hr following arousal. Asterisks represent animals that died within 24 hr of the last measurement shown. Red circles represent the animal whose T_{db} is depicted in Figure 3. The variability of the life span within inbred mice, described by Finch and Tanzi (*25*), is evident in these preliminary observations.

the end of this period that was attributed to an increase in life expectancy associated in part with improved air quality.

Depletion of the at-risk population acts to flatten the exposure–response mortality curve. [Daily mortality can be modeled as the product of the at-risk population times a hazard function that includes air pollution and weather variables (*45*).] Thus, during the winters of 1963–1972 in London, the drop in daily mortality associated with higher levels of air pollution was attributed to depletion of at-risk individuals through prior exposure to lower levels of pollution; the phenomenon was referred to as the "saturation effect" of air pollution (*46*). A similar pattern has also been described in association with PM_{10} across the 90 largest U.S. cities (*14*). Apparently, the saturation effect may occur independently of the absolute levels and physicochemical properties of air pollution. Thus, the levels of PM_{10} and SO_2 in an extensively monitored subset of 20 of the 90 U.S. cities ranged far below the levels of both British smoke, an index of $PM_{2.5}$, and SO_2 in London in the 1960s and 1970s. And whereas acidic SO_4 aerosols were most strongly associated with daily mortality in London, they were not likely to have figured prominently, if at all, among most U.S. cities. "Harvesting," in which time is the independent variable, is another commonly used descriptor of essentially the same phenomenon (*7*).

How premature the deaths associated with air pollution may be is unclear. Both a short-term loss of life expectancy measured in days or weeks (typically referred to as "harvesting") and, of greater concern, a long-term loss caused by cumulative injury from years of exposure and measured in months or longer, may be involved. Distinguishing between the two possibilities remains a critical challenge to research and regulatory policy. We believe the short-term loss is confined to a relatively small group of frail, unstable individuals, whereas the long-term loss implicates the general population, particularly urban dwellers.

The causal agents for the two types of loss are not necessarily the same. Fluctuations in ambient levels of coarse PM (> $PM_{2.5}$) and temperature may both contribute to excess daily mortality. Insofar as reflex cough and bronchoconstriction contribute to daily mortality, coarse PM readily qualify as a proximate cause of death. Coarse PM that manage to penetrate the oronasal passages (their removal rate in the nose is relatively high) deposit preferentially in the larynx and large central airways (*47,48*), where the neural sensors responsive to mechanical stimuli such as insoluble dusts are most abundant (*49, 50*) and where the cumulative surface area is minimal compared with more peripheral regions of the lung (*51*), so the density of dose for any specified mass deposition of PM is highest. Neither fluctuation in coarse PM nor fluctuation in temperature, however, is likely to affect long-term cardiorespiratory health or longevity directly as is postulated for fine PM ($PM_{2.5}$). Coarse PM are formed principally through mechanical forces, whereas fine PM ($\leq PM_{2.5}$) are formed principally through fuel combustion and atmospheric transformations. Compared with coarse PM, they are generally more soluble and acidic, and more likely to contain toxic metals and metastable chemical species, both inorganic and organic (*52,53*).

Time-series analysis has generally been regarded as suitable for identifying only short-term losses. However, the recent development of regression methods reported to be insensitive to such losses has yielded evidence of an effect that may persist at least 300 days (*54*). The latter comports with evidence from a limited number of prospective cohort studies (*55,56*). We would conclude with the following proposition: Although our hypothesis was intended to explain the short-term loss of life associated with daily fluctuations in air quality, the same experimental model might also be used to assess possible long-term consequences. Our premise is that any long-term shortening of life expectancy caused by repeated exposure will be reflected in a demonstrable change in the topography of homeostatic decline as well as survival.

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